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Selective and Gram-scale Synthesis of [6]Cycloparaphenylene

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Dedicated to Professor Peter Vollhardt on the occasion of his 69th birthday

Abstract: The selective, practical and large scale synthesis of [6]cycloparaphenylene ([6]CPP), which is the second smallest CPP synthesized so far, was achieved in nine steps from commercially available starting materials: 1,4-dibromobenzene and 4-bromo-4'-hydroxybiphenyl. The key intermediate, *cis*-1,4-(*p*-bromophenyl)-1,4-bis(triethylsiloxy)-2,5-cyclohexadiene, was prepared on a large scale (>20 g) and was selectively dimerized to form a cyclic precursor of [6]CPP via platinum-mediated assembly and subsequent reductive elimination. Deprotection of the triethylsilyl group and subsequent H₂SnCl₄-mediated reductive aromatization afforded [6]CPP in an overall yield of 23% from commercially available sources with > 1 g scale.

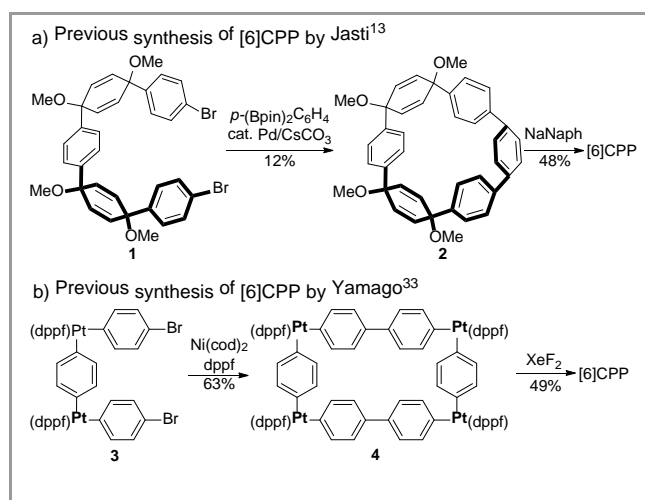
Key words: cycloparaphenylene, cyclization, organometallic reagents, platinum, tin

Cycloparaphenylenes (CPPs, Figure 1) have garnered significant interest due to their unique structure comprising the simplest structural unit of carbon nanotube sidewalls, as well as their vast potential in materials science and technology.¹⁻⁸ Following the first synthesis of [9], [12], and [18]CPPs by Bertozzi and co-workers in 2008,⁹ significant progress has been made toward the synthesis of CPPs with different sizes and their analogues by Jasti,⁹⁻¹⁶ Itami,¹⁷⁻²⁸ Yamago,²⁹⁻³⁵ and others.³⁶⁻⁴³ Accordingly, unique properties of CPPs, e.g., size-dependent photophysical⁴⁴⁻⁵⁰ and redox properties^{31,51-55} and size-complementary host-guest chemistry,⁵⁶⁻⁵⁹ have been revealed.

The synthesis of small CPPs has recently attracted significant attention because smaller CPPs possess narrower HOMO-LUMO energy gaps (HOMO and LUMO refer to the highest occupied molecular orbital and the lowest unoccupied molecular orbital, respectively) than larger CPPs,³¹ which is advantageous for applications in organic electronic materials. For example, [5]CPP, which is the smallest CPP synthesized to date, possesses the most narrow

HOMO-LUMO gap among known CPPs and has a similar energy gap as that of C₆₀.^{34,14} In addition, [5]CPP can be prepared on a large scale.⁶⁰

On the contrary, [6]CPP, the second smallest CPP showing unique crystal packing in the solid state, was prepared by Jasti¹³ and Yamago;³³ however, the reported methods were inefficient for the large-scale preparation of [6]CPP. Specifically, in Jasti's synthesis, cyclic precursor **1**, which bears two *cis*-1,4-dimethoxy-2,5-cyclohexadiene-1,4-diyl units, was reacted with 1,4-diborylbenzene to obtain **2**, which was reductively aromatized using sodium naphthalenide at -78 °C to obtain [6]CPP (Scheme 1a). However, the low coupling efficiency from **1** to **2**, low overall yield (0.7%), and harsh reaction conditions required to form [6]CPP from **2** limit the potential for the large-scale production. In Yamago's synthesis, bis-platinum complex **3** was homocoupled via nickel(0)-mediated Yamamoto coupling^{61,62} to obtain cyclic tetra-platinum complex **4**, and subsequent reductive elimination of platinum gave [6]CPP in 8.7% overall yield (Scheme 1b). Despite the high yield of [6]CPP in this route, the use of four equivalents of platinum limits the practicality of this method.



Scheme 1 Reported syntheses of [6]CPP

We envisioned that *cis*-1,4-dimethoxy-1,4-diaryl-2,5-cyclohexadiene-1,4-diyl **5a** (R = Me), which was

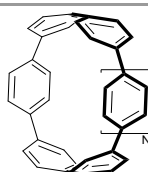
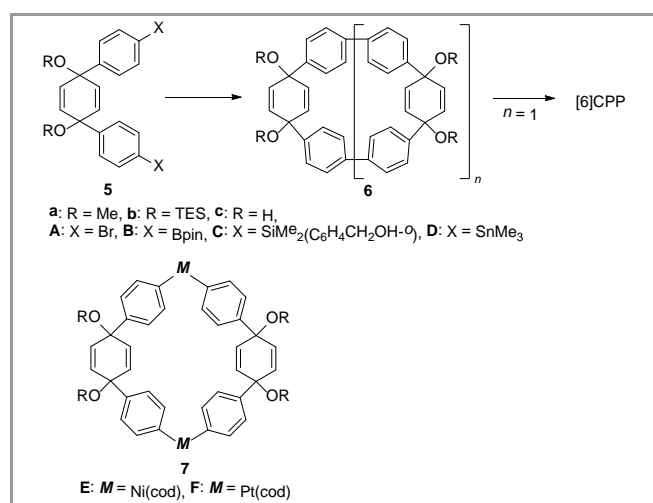


Figure 1 Structure of [N+6]CPP.

used in the syntheses of [9], [12], and [18]CPPs and was prepared in large scale,⁹ would be an excellent precursor for [6]CPP (Scheme 2). If **5a** is dimerized to form the cyclic precursor, reductive aromatization would give [6]CPP. Herein, we report the selective synthesis of [6]CPP based on such strategy. One of the author's group recently reported that *cis*-1,4-dihydroxy-2,5-cyclohexadiene-1,4-diyl served as an excellent masked paraphenylene unit in the synthesis of CPPs and was aromatized under mild conditions.^{34,60} Therefore, triethylsilyl (TES)-protected precursor **5b** (R = TES) was mainly used as a starting material in this study.



Scheme 2 Synthesis of [6]CPP

Cyclodimerization of dibromide **5bA** (R = TES, X = Br) via Yamamoto coupling was examined at first by mixing **5bA** with Ni(cod)₂ (2.0 equiv) and 2,2'-bipyridyl (2.0 equiv) in refluxed THF.^{61,62} After a routine workup, the desired cyclic dimer **6b** (*n* = 1) was isolated in 11% yield (Scheme 2). The corresponding cyclic trimer (*n* = 2) and tetramer (*n* = 3) were also obtained in 31% and 16% yield, respectively. The strain energies of the dimer (*n* = 1), trimer (*n* = 2), and tetramer (*n* = 3) of **6c** (R = H) were calculated to be 95, 9, and 16 kJ mol⁻¹, respectively, using the B3LYP/6-31G* level of theory (see the Supporting Information). Therefore, the formation of a considerable amount of dimer **6b** (*n* = 1), in spite of its high strain energy, suggested that the product formation was kinetically controlled.

The Yamamoto coupling reaction involves the reduction of an aryl halide (ArX) by Ni(0) to form an ArNi(II)X species,⁶³ a disproportionation reaction to form Ar₂Ni(II),^{64,65} and subsequent reductive elimination to obtain the bisaryl product. As the disproportionation reaction is the rate-determining step and the reductive elimination of nickel from bisarylnickel takes place considerably fast, formation of bismetallated, cyclic intermediate **7E** was less likely under the reactions conditions. Therefore, the low selectivity of the coupling reaction must be due to the short life time of the bisarylnickel(II) complex.

Although we examined several different reaction conditions, such as various ligands or solvents, the selective formation of the cyclic dimer could not be achieved.

The platinum-mediated dimerization of **5** was examined next. TES-protected bispinacolborane **5bB** (R = TES, X = Bpin; pin refers to pinacolate)⁶⁰ was treated with Pt(cod)Cl₂ (cod refers to 1,5-cyclooctadiene) (1.0 equiv) and K₃PO₄ (10 equiv) in THF at 60 °C for 84 h, and the desired bisplatinum complex **7bF** (R = TES, M = Pt(cod)) was obtained in 59% yield. Notably, **7bF** was also prepared in 51% yield by mixing bisilane **5bC** [R = TES, X = SiMe₂(C₆H₄CH₂OH-*o*)],⁶⁶ Pt(cod)Cl₂ (1.0 equiv), and K₃PO₄ (5.0 equiv) in THF at 60 °C. The reaction between bis-stannane **5bD** (R = TES, X = SnMe₃) and Pt(cod)Cl₂ was most effective and gave **7bF** in 78% yield. The platinum-mediated dimerization was also successful by mixing a 1:1 mixture of **5aD** (R = Me, X = SnMe₃) and Pt(cod)Cl₂ to give **7aF** in 66% yield. Starting from 4.0 g of **5bD**, 4.5 g of **7aF** was synthesized. The highly efficient formation of **7F** is attributed to the sufficiently long life time and stability of the bisarylplatinum(II) complex to the reductive elimination.

Reductive elimination of platinum from **7bF** was carried out by heating a toluene solution of **7bF** with PPh₃ (4 equiv) at 90 °C for 17 h; the TES-protected cyclic dimer **6b** (*n* = 1) was obtained in 70% yield. We previously reported several conditions for the reductive elimination of platinum in the synthesis of CPPs; however, the use of PPh₃ was the most efficient. Upon treatment of **6b** with tetrabutylammonium fluoride (TBAF), cyclic dimer **6c** (R = H, *n* = 1), bearing two 1,4-dihydroxy-2,5-cyclohexadiene-1,4-diyl units, was obtained quantitatively. More than 4.5 g of **6c** was synthesized. Methoxy-derivative **7aF** was also transformed into **6a** (*n* = 1) in 78% yield by using PPh₃ (4 equiv) at 90 °C for 17 h.

The structure of **6a-c** was characterized using ¹H and ¹³C NMR and ESI-TOF mass spectrometry. In the ¹H NMR spectra, the aromatic protons on the biphenyl bridges were shielded, and were observed around δ = 6.7–6.9 ppm in all compounds, indicating that all compounds possessed similar structures and conformations, where the two biphenyl bridges were in close proximity. The structure of **6a** was unambiguously determined by single crystal X-ray analysis (Figure 2). The biphenyl bridges were about 3.82–4.55 Å apart, and this distance was

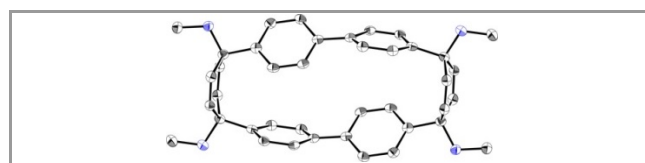


Figure 2 ORTEP drawing of **6a**. Thermal ellipsoids are shown at 50% probability. Hydrogen and solvent atoms are omitted for clarity.

consistent with the shielding effect observed in the ^1H NMR. The biphenyl units were twisted with a dihedral angle in the range of $44.8(4)^\circ$ – $38.5(2)^\circ$. Moreover, all methoxy groups extended outward from the cyclic ring structure, suggesting that protecting groups did not affect the structure of the cyclic skeleton. The structural characteristics clarified by X-ray analysis were consistent with the ^1H NMR data.

Cyclic dimer **6c** was subjected to reductive aromatization with H_2SnCl_4 ,⁶⁰ which was prepared in situ by mixing $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (4.4 equiv) and conc. HCl (8.8 equiv) in THF at room temperature for 22 h. After a routine workup, [6]CPP was isolated in 95% yield following silica gel chromatography. More than 1 g (1.33 g) of [6]CPP was synthesized. As **5bA** was prepared from 1,4-dibromobenzene and 4-bromo-4'-hydroxybiphenyl in four steps and three pots in 64% yield, the overall yield of [6]CPP from commercially available sources was 23%, which was significantly higher than that obtained in previous reports.^{13,33} Reductive aromatization of methoxy-protected **6a** was also carried out using sodium naphthalenide (6.0 equiv) at -78°C for 2 h, although this route was less effective (38% yield) than that from **6c**. These results also clarified the synthetic advantage of the 1,4-dihydroxy-2,5-cyclohexadiene-1,4-diyl precursor for the large-scale synthesis of CPPs.

In summary, we established an efficient and practical synthetic route for [6]CPP. While a stoichiometric amount of platinum was still required, it was substantially less than that required in previously reported method. Furthermore, the mild conditions and high-yielding reductive aromatization step, owing to the use of the dihydroxy-containing precursor, make this synthetic route attractive for the mass production of [6]CPP.

Supporting Information for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>.

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